FDA Briefing Document

Oncologic Drugs Advisory Committee Meeting

February 10, 2010

NDA 22-374
Omacetaxine (Omapro)
ChemGenex Pharmaceuticals

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1 Proposed Indication

Omacetaxine is indicated for the treatment of adults with chronic myeloid leukemia (CML) who have failed prior therapy with imatinib and have the Bcr-Abl T315I mutation.

2 Executive Summary

This NDA submission is based on a single efficacy study, CGX-635-CML-202 (CML-202), in 66 patients with CML who had failure of imatinib therapy and had the T315I mutation.

CML-202 was a multicenter, international, open-label, single-arm trial in 66 patients with CML who had failure of or were intolerant to imatinib and who had the Bcr-Abl T315I mutation. Patients were enrolled and divided into cohorts of chronic phase (CP), accelerated phase (AP) or blast phase (BP) disease. Patients received 1.25 mg/m^2 omacetaxine subcutaneously twice daily for 14 days in a 28-day cycle for up to six induction cycles. If a patient achieved a complete hematologic response (CHR), hematologic improvement or any cytogenetic response, the patient was transitioned to a maintenance schedule of 1.25 mg/m^2 subcutaneously twice daily for 7 days in a 28-day cycle. Complete blood counts were performed weekly in the induction cycles, and bone marrow evaluations were conducted at baseline and every three months while on study.

The primary efficacy endpoint for CP patients was major cytogenetic response (MCyR), consisting of complete cytogenetic response (CCyR) and partial cytogenetic response (PCyR), or CHR. The primary efficacy endpoint for AP and BP patients was MCyR or major hematologic response (MaHR), consisting of CHR, no evidence of leukemia (NEL) or return to chronic phase (RCP). An independent Data Monitoring Committee consisting of two hematologists adjudicated all responses for the primary efficacy analysis.

Efficacy
For the chronic phase cohort of 40 patients, the MCyR rate was 15% (10% CCyR + 5% PCyR) with a median of duration of response of 7.7 months. For the accelerated phase cohort of 16 patients, the MCyR rate was 6.3% and CHR rate was 31.3% with a median of duration of response of 22 weeks. There were no responders in the BP cohort.

Safety
The safety of omacetaxine was evaluated in 131 patients including 66 patients of study CML-202. One hundred and twenty-nine (97%) of these patients had ≥ 1 Treatment Emergent Adverse Events (TEAEs) with 111 (85%) having ≥ one CTCAE grade 3 or 4 TEAEs. Most common AEs were thrombocytopenia (60%), anemia (49%), diarrhea (43%), neutropenia (38%), fatigue (31%), pyrexia (30%), nausea (27%), asthenia

(21%), headache (19%), arthralgia (17%), cough (17%), peripheral edema (16%), injection site erythema (16%), constipation (15%), and anorexia (15%). Most common grade 3 and 4 AEs were thrombocytopenia (55%), anemia (34%), and neutropenia (35%).

One hundred and eighty-one SAEs were reported in 78 (60%) patients. Thirty-eight (54%) of these patients had CP-CML,19 (53%) had AP-CML and 21 (84%) had BP-CML. The most frequent SAEs were febrile neutropenia (11%), thrombocytopenia (11%), bone marrow failure (8%) and anemia (4%).

3 Issues with the submission

FDA would like to seek advice from the ODAC members on the following issues:

Issue #1: Clinical significance of response rate and duration of response

- Study CML-202 was planned to enroll 100 patients. However, the NDA submission only included the efficacy data from 66 patients. The Applicant continued to enroll additional patients after the data cut-off for these 66 patients.
- The indication sought for omacetaxine is for the treatment of CML patients with Bcr-Abl T315I mutation. However, there is no commercially available assay for the detection of this mutation and the Applicant has not submitted any data related to the assay methods to FDA's CDRH.
- Thirty-five percent of patients had no confirmation of Bcr-Abl T315I mutation status by the central laboratory at the time of enrollment, a required study entry criterion.
- The response rate observed in the efficacy study was low. For the chronic phase cohort of 40 patients, the MCyR rate was 15% (10% CCyR + 5% PCyR) with a median duration of response of 7.7 months. For the accelerated phase cohort of 16 patients, the MCyR rate was 6.3% and CHR rate was 31.3% with a median of duration of response of 22 weeks. There were no responders in the BP cohort.

ODAC advice is sought on the adequacy of the sample size and the clinical significance of the observed responses and their duration for the intended patient population.

Issue #2: Benefit:risk ratio

ODAC advice is sought on whether the benefit:risk ratio is favorable for omacetaxine treatment in patients with CML with the T315I mutation whose disease is resistant to or who are intolerant of imatinib.

4 Background

4.1 CML

CML is a relatively rare hematologic malignancy in adults, with approximately 5000 new cases diagnosed annually in the United States.[1] CML results from the neoplastic transformation and proliferation of a hematopoietic stem cell, and the disease affects all hematopoietic cell lineages.[2] CML is characterized by the presence of the Philadelphia (Ph) chromosome, which results from a reciprocal translocation between the long arms of chromosomes 9 and 22 and leads to the formation of the *BCR-ABL* fusion gene. Its product, Bcr-Abl protein, is a constitutively active tyrosine kinase protein that causes the disordered myelopoiesis found in CML.

CML progresses through three phases: an initial chronic phase (CP), a variably defined accelerated phase (AP), and a final blast crisis or acute leukemic phase (BP). Transition from CP to AP and later BP may occur gradually over a period of one year or more or may be more rapid in the form of a blast crisis.

Although there is no single, universally accepted classification system for chronic versus accelerated versus blast phase, the following two classification systems are often used for such a purpose.

The World Health Organization (WHO) classifies the phases as follows:[3]
CML, accelerated phase (AP)

- Diagnose if one or more of the following is present:
    - Blasts 10% to 19% of peripheral blood white cells or bone marrow cells
    - Peripheral blood basophils at least 20%
    - Persistent thrombocytopenia (<100 $x10^9$/L) unrelated to therapy, or persistent thrombocytosis (>1000 $x10^9$/L) unresponsive to therapy
    - Increasing spleen size and WBC count unresponsive to therapy
    - Cytogenetic evidence of clonal evolution (i.e., the appearance of an additional genetic abnormality that was not present in the initial specimen at the time of diagnosis of chronic phase CML)
    - Megakaryocytic proliferation in sizable sheets and clusters, associated with marked reticulin or collagen fibrosis, and/or severe granulocytic dysplasia, should be considered as suggestive of CML-AP. These findings have not yet been analyzed in large clinical studies, however, so it is not clear if they are independent criteria for accelerated phase. They often occur simultaneously with one or more of the other features listed.

CML, blast phase (BP)

- Diagnose if one or more of following is present:
    - Blasts $\geq$20% or more of peripheral blood white cells or bone marrow cells

- Extramedullary blast proliferation
- Large foci or clusters of blasts in bone marrow biopsy

The International Bone Marrow Trial Registry defines advanced CML as:[4]

- WBC difficult to control (> 50 x 10^9/L)
- Rapid doubling of WBC (< 5 days)
- ≥10% blasts in peripheral blood or bone marrow
- ≥20% blasts + promyelocytes in peripheral blood or bone barrow
- ≥20% basophils + eosinophils in peripheral blood
- Anemia or thrombocytopenia unresponsive to busulfan or hydroxyurea
- Persistent thrombocytopenia (>1000 x 10^9)
- Cytogenetic changes in addition to single Ph chromosome
- Increasingly splenomegaly
- Chloromas
- Marrow fibrosis
- Previous episode of blastic phase (>30% blasts)

4.2 CML Treatment

Prior to imatinib's approval, treatment included single-agent therapy with interferon, hydroxyurea, or busulfan. With the advent of tyrosine kinase inhibitors (TKIs), the treatment regimen and disease course of CML has been altered. Allogeneic hematopoetic stem cell transplantation (HSCT) was and still is considered only curative therapy for patients with CML.

The treatment landscape has evolved significantly with the understanding of CML biology and the advent of tyrosine kinase inhibitors (TKI) that specifically inhibit the Bcr-Abl kinase.

Imatinib was granted:

- Accelerated approval (AA) in 2001 for the treatment of patients with CP-, AP, and BP CML after failure of IFN, based on Major Cytogenetic Response (MCyR) and Complete Hematologic Response (CHR)
- AA in 2002 for the treatment of patients with newly diagnosed CML
- Regular approval in 2003 for second-line indication (converted from AA), based on durable responses: at 2 years 88% of patients with CP-CML who achieved MCyR maintained their responses; 85% were free of progression to AP or BP, and estimated overall survival (OS) was 91%.

4.3 Treatment of imatinib-resistant and intolerant CML

Dasatinib, the second Bcr-Abl inhibitor, received AA in 2006 for treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid

leukemia (CML) with resistance or intolerance to prior therapy including imatinib and for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy based on major cytogenetic response in chronic phase and major hematologic response in accelerated and blast phases.

Nilotinib, the third and most recent Bcr-Abl inhibitor, received its AA in 2007 for the treatment of CP and AP Ph+ CML in adult patients resistant or intolerant to prior therapy that included imatinib.

4.3.1 Primary endpoints for prior approvals

Table 1 below summarizes the primary endpoints that have been used for drug approvals for the treatment of patients with imatinib-resistant or intolerant CML.

Table 1 Prior approvals for imatinib-resistant or intolerant CML

Primary endpoint		Dasatinib		Nilotinib	
		N	Response Rate (95% CI)	N	Response Rate (95% CI)
CML-CP: MCyR		167	63% (56-71)	232	40% (33-46)
CML-AP:	MaHR	158	66% (59-74)	---	---
	MCyR		39% (31-47)		
CML-BP	Myeloid Blast: MaHR MCyR	75	 28% (18-40) 28% (18-40)	---	---
	Lymphoid Blast: MaHR MCyR	33	 42% (26-61) 52% (34-69)		

For CML chronic phase, the primary endpoint of MCyR has been used in the approval of dasatinib and nilotinib, whereas MaHR and MCyR were used for the approval of dasatinib for CML in AP or BP. The decision to approve imatinib and dasatinib was also based on duration of response.

4.4 Bcr-Abl T315I mutation

CML patients who have the Bcr-Abl T315I mutation appear to be resistant to the three approved TKIs. The threonine-to-isoleucine change at amino acid position 315 is located within the ATP binding site and the activation loop of c-Abl that are required for TKI binding.[5] A recently published epidemiological study described a retrospective review of 222 patients with the T315I mutation and calculated overall survival and progression-free survival rates of these patients from the time of diagnosis, the time of first TKI failure and the time of T315I mutation detection.[6]

Table 2. Survival of patient with T315I mutation[6]

Survival since 1st time of TKI resistance, by phase at the time of TKI resistance				
CML CP		CML AP	CML BP	Ph+ALL
(N=88)		(N=34)	(N=54)	(N=46)
Median follow up months	27.7	19.8	6.2	4.8
Median OS Months (95% CI)	51.4 (44.4-59.5)	49.4 (15.2-52.0)	8.3 (4.6-11.3)	6.3 (5.0-12.2)
1-year OS Rate (95% CI)	93% (85-97%)	72% (54-85%)	35% (22-48%)	37% (22-53%)
Median PFS Months (95% CI)	17.2 (12.9-27.1)	10.8 (5.3-34.0)	3.6 (2.3-5.4)	4.6 (2.3-5.2)
1-year PFS Rate (95% CI)	66% (55-75%)	48% (30-64%)	19% (9-30%)	18% (7-32%)
Survival since T315I mutation detection, by phase at T315I mutation detection				
CML CP		CML AP	CML BP	Ph+ALL
(N=82)		(N=38)	(N=56)	(N=46)
Median follow up months	12.4	15.2	3.0	3.6
Median OS Months (95% CI)	22.4 (18.2-48.5)	28.4 (15.9-49.8)	4.0 (2.0-5.0)	4.9 (3.4-7.3)
1-year OS Rate (95% CI)	71% (58-80%)	69 (50-81%)	23% (13-36%)	12% (3-27%)
Median PFS Months (95% CI)	11.5 (9.2-15.7)	22.2 (9.0-N/A)	1.8 (1.2-4.0)	2.5 (1.8-3.6)
1-year PFS Rate	46% (34-57%)	56% (38-70%)	16% (7-27%)	7% (1-19%)

These patients had failure of first-line therapy with imatinib. Median time between TKI treatment initiation and T315I mutation detection was 29.2, 15.4, 5.8, and 9.1 months, respectively, for CP, AP, BP, and Ph^+ ALL patients. After T315I mutation detection, second-generation TKIs were used in 56% of cases, hydroxyurea in 39%, imatinib in 35%, cytarabine in 26%, MK-0457 in 11%, stem cell transplantation in 17%, and interferon-alpha in 6% of cases. Table 2 above describes the survival for these patients with T315I mutations. The authors concluded that, much like patients without the T315I mutation, survival was dependent on the disease phase at the time of mutation detection.

The reported T315I mutation frequency in imatinib-resistant chronic myeloid leukemia (CML) patients ranges between 2% and 20%, depending on the detection methods as well as patient cohort characteristics and treatment variability. It is estimated 250 to 300 CML patients are diagnosed with the T315I mutation per year in the US.

4.5 Treatment of CML patients with T315I mutation

Currently, there is no approved therapy for these patients, although hydroxyurea has been used with variably reported response rate and HSCT remains a treatment option if patients are eligible.

4.6 Major Regulatory Milestones for Omacetaxine Development

On April 16, 2001, IND #062384 was activated to study homoharringtonine (HHT, later changed to omacetaxine) in humans under the sponsorship of ChemGenex Pharmaceuticals, Ltd. HHT previously had been investigated under IND #019125 by the National Cancer Institute as the sponsor.

In January 2005, ChemGenex requested fast track designation for HHT; however, this request was denied because the sponsor “ha[d] not yet submitted sufficient data demonstrating the efficacy of HHT in patients with chronic myelogenous leukemia (CML) who have failed imitanib treatment or outlined a development plan.”

ChemGenex submitted a Special Protocol Assessment (SPA) request for Study CGX-635-CML-203 in December 2005. The SPA was denied based on the inadequacy of trial design in terms of defining the patient population, the appropriateness of the primary endpoint and the single-arm trial design.

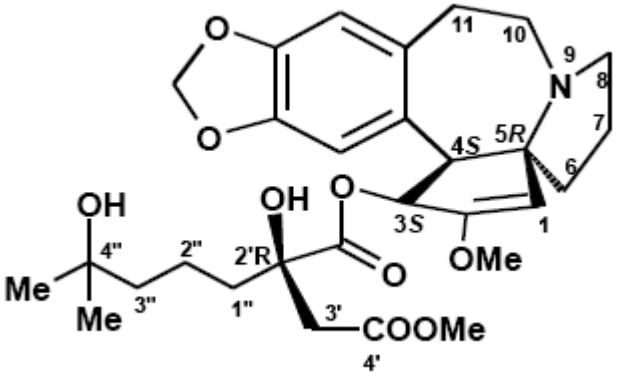
ChemGenex requested a meeting with the Agency in October 2006 to discuss the statistical plan and design of the trial CGX-635-CML-202 (CML-202), which was intended to support approval of an NDA for HHT. The major discussion points were regarding appropriate primary endpoints for response in the different phases of CML as well as assumptions about the response rate in determining the sample size. FDA emphasized that the appropriate primary endpoint for CML-CP should be major cytogenetic response and that major hematologic response can be used for AP and BP patients.

In March 2006, ChemGenex received orphan drug designation for omacetaxine for treatment of CML, and the Applicant received fast track designation for CML patients with T315I mutation in November 2006.

5 Drug Description

Omacetaxine mepesuccinate (also known as homoharringtonine, or HHT) is a New Molecular Entity (NME) and is the first in class of cephalotaxines. It is a semi-synthetic product derived from the Chinese evergreen tree (*Cephalotaxus fortunei*). The chemical name of omacetaxine is cephalotaxine, 4′-methyl (2′R)-hydroxyl-2′-(4″-hydroxyl-4″-methylpentyl) butanedioate (ester), [3(R)].

Figure 1 Structural formula of omacetaxine mepesuccinate



6 Study CML-202

Study Title: A Phase II Open-Label Study of the Subcutaneous Administration of Omacetaxine (CGX-635) in the Treatment of Patients with Chronic Myeloid Leukemia (CML) with the T315I Bcr-Abl Gene Mutation.

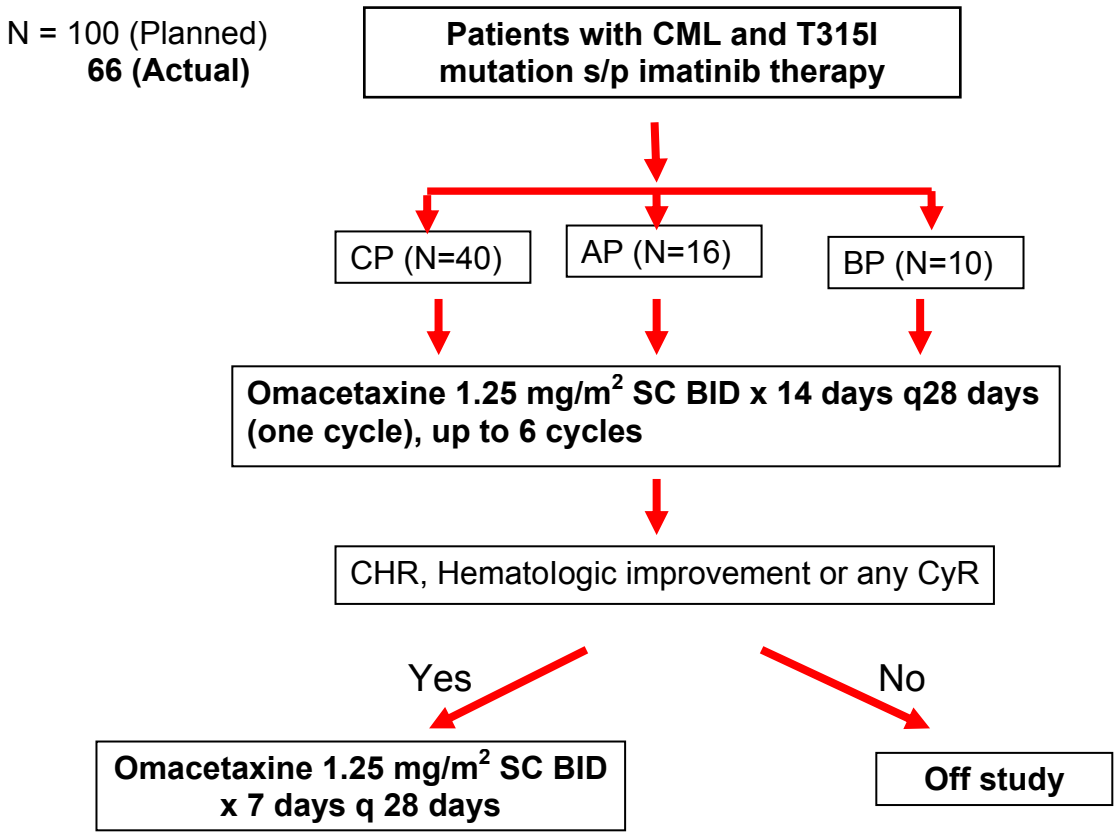
Objectives:

The primary objective of the study was to evaluate the safety and efficacy of subcutaneous administration of omacetaxine in achieving a clinical response in CML patients in CP, AP, or BP who have failed prior treatment with imatinib mesylate and have the Bcr-Abl T315I gene mutation.

6.1 Study Design

The study was an open label, multi-center Phase 2 trial of omacetaxine in patients with CML who had failure of or who were intolerant of imatinib and who had the Bcr-Abl T315I mutation.

Figure 2 Study design schema



6.2 Study Drug administration and schedule

Patients received induction cycles of 1.25 mg/m^2 omacetaxine subcutaneously twice daily for 14 days in a 28-day cycle for up to six induction cycles. If a patient achieved a CHR, hematologic improvement or any cytogenetic response, the patient was transitioned to a maintenance schedule of 1.25 mg/m^2 subcutaneously twice daily for 7 days in a 28-day cycle.

6.3 Duration of treatment

Patients continued to receive omacetaxine until one of the following was met:

1) Failure to achieve a meaningful hematologic or cytogenetic response. Patients who did not demonstrate evidence of clinical response after six cycles were considered for removal from the study, although with permission of the sponsor's

medical monitor, treatment could continue, if clinically indicated, provided there was no evidence of toxicity Grade 3 or above.
2) An excessive Grade 3-4 toxicity without a response to treatment or occurrence of any other AE, intercurrent illness or laboratory abnormality.
3) Treatment with a prohibited concomitant medication, other than the use of appropriate medications for the treatment of AEs under the direction of the principal investigator.
4) Patient noncompliance, defined as refusal or inability to adhere to the study schedule.
5) At the request of the patient, principal investigator, the sponsor, or regulatory authority.
6) Patient was lost to follow-up.
7) Patient death.

6.4 Study Endpoints

The primary efficacy endpoint was CHR and/or MCyR for chronic phase patients, and CHR, no evidence of leukemia (NEL), return to chronic phase (RCP) and/or MCyR for accelerated and blast phase patients.

Secondary efficacy endpoints included degree of suppression of Bcr-Abl transcript levels; reduction in the proportion of Bcr-Abl T315I mutation from baseline; the number of cycles and cumulative number of doses of omacetaxine to achieve the best clinical response; progression-free survival and overall survival.

6.5 Major eligibility criteria

1. Ph+ CML in either CP, AP, or BP with loss of hematologic or cytogenetic response on current or most recent therapy
2. CML- AP:
    a. ≥ 15-<30% blasts in PB or BM
    b. ≥ 30% blasts + promyelocytes in PB or BM
    c. ≥ 20% basophils in PB or BM
    d. platelet count < 100 × 10^9/L unrelated to therapy
    e. clonal evolution.
3. CML-BP: ≥ 30% blasts in the peripheral blood or bone marrow or presence of extramedullary disease other than spleen or liver.
4. Failure of prior imatinib therapy:
    a. No CHR by 12 weeks (whether lost or never achieved)
    b. No cytogenetic response by 24 weeks (i.e., 100% Ph+) (whether lost or never achieved)
    c. No MCyR by 52 weeks (i.e., ≥ 35% Ph+) (whether lost or never achieved)
    d. Progressive leukocytosis

5. Hydroxyurea permitted immediately prior to and during the first two cycles for patients with rapidly proliferating disease
6. Presence of the T315I Bcr-Abl gene mutation.

6.6 Primary endpoint evaluation

Efficacy: Response assessment was conducted by an independent central review using the criteria outlined below. Investigator assessment of response also was collected, but not used for efficacy analysis.

6.6.1 Evaluation Methods

- Bone marrow aspiration and cytogenetic analysis, every 3 months
- Complete blood count, before each dosing and weekly during the 14-day dosing
- Clinical Evaluation

6.6.2 Schedule of evaluations (Table 3 below)

Bone marrow aspiration was needed to confirm the responses.

Table 3. Treatment and Evaluation Schedule

Activity	Screening	Preceding each dosing cycle[a]	Every 3 months on study[b]	Study completion, unscheduled visits, or early termination[c]
Informed consent/entry criteria/medical history/ height	X			
Physical exam/weight	X	X		X
Calculate body surface area	X	X		
Vital signs	X	X[d]		X
Chest x-ray	X[e]			
ECG	X[e]	X[f]	X[f]	X[f]
Hematology[g,i]	X	X[g]	X	X
Serum chemistry[h,i]	X	X[g]	X	X
Bone marrow aspiration and cytogenetics[j]	X		X[k]	X[l]
Bcr-Abl quantitative transcript levels by RT-PCR[m]	X	X		X[l]
Bcr-Abl mutation analysis[n]	X		X[o]	X
Urinalysis; urine or serum pregnancy test[p]	X			
Document other measures of disease and disease symptoms	X	X		X
ECOG performance status	X	X		X
Drug accountability/ AE reporting		X		X
Concomitant medication	X	X		X
Omacetaxine dosing twice daily[q]		-	-	

[a] Physical exam, weight, and clinical laboratory assessments were obtained on the day of or within 3 days prior to start of the treatment cycle. Results were reviewed prior to initiating a treatment cycle. Screening studies were substituted for the initial treatment course if acceptable results were obtained within 7 days of Treatment Cycle 1.
[b] Additional studies were conducted earlier than a scheduled 3-month interval if clinically indicated, e.g., a rising level of Bcr-Abl transcript was observed. For patient convenience, assessments may have been scheduled every 3 cycles (rather than exactly every 3 months).
[c] Additional physical exam, laboratory tests, and other diagnostic studies including bone marrow aspirations, biopsies, cytogenetics and quantitative PCR studies (in patients achieving complete cytogenetic response [CCyR]) were conducted at scheduled and non-scheduled time points to evaluate safety and disease status, as was clinically indicated.
[d] Vital signs (heart rate, blood pressure, respiratory rate, and temperature) measured < 30 min. pre-injection of omacetaxine and 20 min. post injection on Day 1 of each treatment cycle. If the patient had hypotension (systolic blood pressure < 90 mm Hg), vital signs were taken and recorded more frequently, until the patient had stabilized. (In the case of outpatient injections, some time points were omitted if logistically not possible, e.g., the time point occurred over the weekend).
[e] Chest x-ray and ECG were omitted if prior studies were available within the preceding 1 month.
[f] Electrocardiogram prior to cycles 1 – 3 and optionally after completion of Day 14 of treatment cycle 1, if the patient was available for this exam. Repeat ECG every 3 months during therapy, at study completion, unscheduled visits, or early termination. In Germany, ECGs were done before and after every omacetaxine treatment cycle.
[g] Complete blood counts included hematocrit, hemoglobin, red blood cells, WBC, differential, and platelet count.
[h] Chemistry included glucose, blood urea nitrogen, creatinine, uric acid, total bilirubin, and alanine aminotransferase.
[I] Every 7 days during initial therapy. For subsequent cycles, every 14 days and prior to the start of each treatment cycle; assessments were obtained more frequently if clinically indicated. If lab values demonstrated a predictable trend and it was deemed clinically acceptable, the frequency of laboratory studies were reduced to only on Day 1 of subsequent treatment cycles, preceding the omacetaxine injection.

[j] Bone marrow exam with cytogenetic analysis was performed by the G-banding technique. Marrow specimens were examined on direct short-term (24-hour) cultures; at least 20 metaphases were analyzed. Bone marrow and cytogenetic analysis were omitted at screening if they were done in the preceding 1 month, or greater, if the baseline cytogenetic analysis performed remained an appropriate baseline measurement and the patient had not received anti-leukemic therapy during this period (other than palliative therapy e.g., hydroxyurea). Assessments were also performed to confirm cytogenetic response.
[k] In patients who achieved a CHR or MCyR during initial therapy, the response was confirmed by a repeat CBC, bone marrow aspiration (for patients with a hematologic response), cytogenetics of the bone marrow aspirate (for patients with a cytogenetic response), and Bcr-Abl transcript levels by qRT-PCR of peripheral blood, at the intervals specified below. For patient convenience, confirmatory studies were scheduled prior to the next scheduled omacetaxine treatment cycle (rather than exactly at 4 or 8 weeks, as specified below, after the initial response).
(1) Chronic phase CML: response confirmed ≥ 8 weeks after the initial documentation of the response, i.e., ≥ 8 weeks after the patient first met the clinical and laboratory criteria for a response
(2) Accelerated and BP CML: response confirmed ≥ 4 weeks after the initial documentation of the response, i.e., ≥ 4 weeks after the patient first met the clinical and laboratory criteria for a response
[l] Bone marrow aspiration/biopsy if indicated ± cytogenetics (optional).
[m] Bcr-Abl quantitative transcript levels obtained by quantitative PCR analysis of peripheral blood in patients achieving a CCyR. Bcr-Abl transcripts were detected by real-time qRT-PCR analysis on peripheral blood.
[n] as described in the protocol.
[o] All patients. Additional studies were conducted earlier than a scheduled 3-month interval if clinically indicated, e.g., a rising level of Bcr-Abl transcript was observed.
[p] Females of child-bearing potential.
[q] The initial therapy was 1.25mg/m2 twice daily for 14 consecutive days every 28 (+ 3) days; the number of dosing days for subsequent cycles was adjusted such that hematologic recovery would support a 28-day dosing regimen.

6.7 Safety Evaluation

Safety assessments included physical exams, clinical laboratory values, and treatment-emergent AEs. AEs were coded by body system using a medical dictionary for regulatory authorities (MedDRA®) and were graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) scale, Version 3.0.

6.8 Evaluation Criteria

Response criteria

Cytogenetic response: Response to be confirmed by a repeat cytogenetics of the bone marrow aspirate per protocol.

- CCyR: 0% Ph+ cells in at least 20 metaphases examined
- PCyR: 1-35% Ph+ cells in at least 20 metaphases examined

Hematologic response:

- Complete hematologic response
    - For CML-CP patients, only the peripheral hematologic results were necessary for assessment of response; for CML-AP and CML-BP patients, both the peripheral blood and bone marrow assessments were required
    - CP
        - WBC < 10 X 10^9/L
        - Platelets < 450 X 10^9/L
        - Myelocytes + metamyelocytes < 5% in blood
        - No blasts or promyelocytes in blood
        - < 20% basophils in blood
        - No extramedullary disease
    - AP/BP
        - Absolute neutrophil count ≥ 1.5 X 10^9/L
        - Platelets ≥ 100 X 10^9/L
        - No blood blasts
        - Bone marrow blasts < 5%
        - No extramedullary disease
- No evidence of leukemia (NEL): Morphologic leukemia-free state defined as <5% bone marrow blasts
- Return to Chronic Phase (RCP)
    - < 15% blasts in bone marrow and peripheral blood
    - < 30% blasts + promyelocytes in bone marrow and peripheral blood
    - < 20% basophils in peripheral blood
    - No extramedullary disease other than spleen and liver

7 Study Results

Study results were based on the database cut-off date of March 9, 2009 and updated cut-off date of September 17, 2009.

7.1 Patient Population

Efficacy: Sixty-six patients on study CML-202 were enrolled between September 2006 and March 2009 globally with 29 (44%) from North America and 37 (56%) from Europe and Asia.

Safety: The safety analysis was performed on 131 patients who received ≥ 1 dose of Omacetaxine (see section 7.3).

7.2 Efficacy (study CML-202)

7.2.1 Patient characteristics

Table 4 lists patient demographics. There were 46 (70%) males and 20 (30%) females, and the median age at enrollment was 58. All 66 patients had received prior tyrosine kinase inhibitor (TKI) therapy with imatinib.

Table 5 shows the TKIs patients had received prior to the enrollment. Fourteen (21.2%) patients had received only imatinib; 34 (51.5%) patients had received at least one additional TKI for a total of two; 15 (22.7%) patients had received at least two additional TKIs for a total of three; and three patients (4.5%) had received more than three TKIs total.

Table 4 Patient Demographics

Cohort	Chronic N=40	Accelerated N=16	Blast N=10	Total N=66
Median age (years)	59	62	50	58
Sex Male (%) Female (%)	 28 (70) 12 (30)	 11 (69) 5 (31)	 7 (70) 3 (30)	 46 (70) 20 (30)

Table 5 Previous TKI Therapy

Cohort	Chronic N=40	Accelerated N=16	Blast N=10	Total N=66
1 TKI (%) (imatinib only)	12 (30)	1 (6.3)	1 (10)	14 (21.2)
2 TKIs* (%)	20 (50)	8 (50)	6 (60)	34 (51.5)
3 TKIs (%)	6 (15)	6 (37.5)	3 (30)	15 (22.7)
>3 TKIs (%)	2 (5)	1 (6.3)	0	3 (4.5)

7.2.2 Assay issues for the mutation detection

- Methods of detection of T315I mutation were different from each other, depending on whether they were performed at MDACC in Texas, or in Germany. In addition, the mutation status was not confirmed in 35% of patients prior to the onset of the study treatment.

  The presence of T315I mutation was a required eligibility criterion. Two central laboratories evaluated patient samples for the presence of this mutation using different methods as noted below:
  - University of Texas MDACC, Houston, TX
    - qRT-PCR and rapid pyrosequencing
  - Medizinische Universitätsklinik, Mannheim, Germany
    - Denaturing high-performance liquid chromatography.

  Table 6 details whether patients had their T315I mutation status confirmed at baseline by one of the central laboratories. Forty-three (62.5%) patients had central laboratory confirmation at baseline; 11 (16.7%) patients did not have central laboratory confirmation, and 12 (18.2%) patients did not have bone marrow samples sent to the central laboratory at baseline.

Table 6 Central Laboratory Confirmation of T315I Status at Baseline

Central testing	Chronic N=40	Accelerated N=16	Blast N=10	Total N=66
Yes (%)	28 (70)	8 (50)	7 (70)	43 (62.5)
No (%)	7 (17.5)	3 (18.8)	1 (10)	11 (16.7)
Not done (%)	5 (12.5)	5 (31.3)	2 (20)	12 (18.2)

As can be seen from Table 6, the T315I mutation status was not confirmed in 23 patients (35%) at the onset of the study treatment.

- The Applicant had not submitted any data related to the T315I mutation detection methods to the FDA's Center for Devices and Radiological Health by January 2010.

7.2.3 Primary endpoint result --- Response Rate

The Applicant reported the following response rates by disease phase:

- CP: 25% MCyR (6 CCyR + 4 PCyR) and 85% CHR
- AP: 6.3% MCyR (1 CCyR) + 37.5% MaHR (5 CHR + 1 RCP)
- BP: 30% MaHR (2 CHR + 1 RCP)

A summary of the FDA evaluation of response based on the review of the source data including case report forms (CRF) is presented in Table 7 below.

Table 7 FDA's Summary of Response Based on Review of Source Data

Cohort	Chronic N=40	Accelerated N=16	Blast N=10
CCyR 95% CI	4 (10%) (3.3, 24.8)	1 (6.3%) (0.7, 35.6)	0
PCyR 95% CI	2 (5%) (1.0, 18.9)	0	0
CHR 95% CI	NA	5 (31.3%) (12.0, 59.0)	0
NEL	NA	0	0

*All 95% CIs are exact binomial CIs

In the chronic phase cohort, the Applicant reported a MCyR of 25%. However, among the six CCyRs reported, two were unconfirmed due to the lack of protocol-required bone marrow aspirations. Additionally, out of the four PCyRs reported, two were unconfirmed. One of these two patients did not have subsequent bone marrow evaluation; the other did have a subsequent bone marrow evaluation which demonstrated that 100% of the cells examined were Philadelphia chromosome-positive. Thus, the observed MCyR rate is 15% in the chronic phase cohort (10% CCyR + 5% PCyR).

In the accelerated phase cohort, FDA confirmed the findings of 1 CCyR and 5 CHRs.

In the blast phase cohort, the Applicant reported two CHRs.

- One patient with an adjudicated CHR was enrolled in the BP cohort based on BM blasts >30%. An adjudicated response on D14 of therapy was based only on peripheral blood (PB) and not on bone marrow (BM) evaluation. There was no simultaneous evaluation of PB and BM that demonstrates absence of peripheral blasts and normal BM blasts. The patient discontinued the study treatment due to disease progression after 7 cycles. Therefore, FDA does not consider this patient as a true responder.
- The second patient with an adjudicated CHR was enrolled in the BP cohort based on extramedullary disease. An adjudicated response of CHR

was recorded at the time of the first CBC after therapy was initiated. However, there was no description of resolution in this patient's CRFs for the extramedullary disease, and no bone marrow evaluation was performed. The patient received three cycles of therapy and died soon after completion of third cycle. Therefore, FDA does not consider this patient as a true responder.

7.2.4 Duration of Response

Table 8 depicts the duration of responses originally reported by the Applicant. The duration of response for CP patients was 7.7 months according to the Applicant's updated data and was confirmed by FDA review.

However, for the patients in the accelerated phase cohort, the duration of response per FDA review is shorter than that presented by the Applicant. Three of the five patients who were reported to have achieved CHR (confirmed by FDA review) were enrolled in the AP cohort based only on increased basophils in peripheral blood. The Applicant's definition of CHR for AP did not include the criterion that basophils in peripheral blood must be < 20%, as in the study cited in dasatinib labeling. All three patients who were reported to have achieved CHR per adjudicated response still had their basophil counts > 20% in the peripheral blood. When FDA used the basophil counts < 20% as the response criterion, the duration of response was shorter in these patients.

Table 8 Applicant's Table of Duration of Response

	Cohort		
	CP (N=40)	AP (N=16)	BP (N=10)
Duration of HR			
N	34	6	3
Median (mos.)	10.0	6.6	2.2
Min, Max	1.7, 30.0	1.7, 14.8	1.2, 4.4
Duration of MCyR			
N	10	1	0
Median (mos.)	5.6	8.3	NA
Min, Max	2.1, 14.1	8.3, 8.3	NA

Additionally, patients who achieved an adjudicated response of CHR frequently did not have bone marrow evaluations accompanying the protocol-required complete blood count. In the accelerated phase cohort,

four out of the five patients who achieved CHR eventually had a bone marrow evaluation confirming CHR. However, one patient never had a confirmatory bone marrow evaluation.

Furthermore, two of the five accelerated phase patients were lost to follow up, though the Applicant has recorded the response as ongoing. Table 9 and Table 10 summarize the duration of response according to FDA's review compared to that reported by the Applicant.

Table 9 Duration of Response in Accelerated Phase Cohort

AP patients	Response per Applicant n=5	Response per FDA: PB only n=5	Response per FDA PB + BM n=4*	Response per FDA: PB + BM n=5
Median (weeks)	57.1	33.0	22.0	22.0
Mean (weeks)	55.7	26.9	22.4	17.9
Min, Max	39, 78.4	7.1, 40	9.6, 36	0, 36

* does not include patient who did not have a bone marrow evaluation

Table 10 Duration of Response Per Patient in Accelerated Phase Cohort (in weeks)

Patient ID	Applicant response (n=5)	FDA response: PB only (n=5)	FDA response: PB + BM (n=4)	FDA response: PB + BM (n=5)
1	57.1	7.1	NA	0
2	39.0	37.0	22.0	22.0
3	64.1	33.0	22.0	22.0
4	40.0	40.0	36.0	36.0
5	78.4	17.6	9.6	9.6

7.2.5 Reliability of response determination and its duration for individual patients

In the AP and BP cohorts, the per protocol response criteria for CHR stated that the both the peripheral blood and bone marrow must be evaluated for a response of CHR to be meaningful, However, among the five patients who had an adjudicated response of CHR in the AP cohort, none had a bone marrow evaluation at the time that CHR was assigned by the independent review committee. Four of the five patients subsequently had a bone marrow evaluation confirming CHR, whereas one patient never had a confirmatory bone marrow evaluation. This impacted assessment of response duration for these patients. Assessment for extramedullary disease was not performed for the single patient in blast phase cohort who responded according to the applicant.

7.3 Safety

7.3.1 Safety population

Table 11 lists all studies submitted in this application. Patients from study CML-202 (with T315I mutation) and study CML-203 (refractory to TKI without T315I mutation) form the core population for the safety analysis of omacetaxine. Study CML-203 used the same dosing regimen as CML202. This core safety population, referred to as study group 2 (SG2), consisted of 66 patients in CML-202 as described above (40 with chronic phase, 16 with accelerated phase and 10 with blast phase CML) and 65 patients on CML-203 (30 with chronic phase, 19 with accelerated phase and 15 with blast phase CML) for a total of 131 patients.

Table 11 Omacetaxine Studies (Subcutaneous Administration)

Study ID	Design	Regimen	# of subjects
CML-202 **(Primary Study)**	Phase II, open label, multicenter Study	**Induction:** 1.25 mg/m² twice daily for 14 consecutive days every 28 (±3) days **Maintenance:** 1.25 mg/m^2 twice daily for 7 days every 28 (±3) days	66
CML-203 **(Secondary Study)**	Phase II, open label, multicenter Study	**Induction:** 1.25 mg/m² twice daily for 14 consecutive days every 28 (±3) days **Maintenance:** 1.25 mg/m^2 twice daily for 7 days every 28 (±3) days	65
04.2/04.3	**Study 04.2**: Phase II, multicenter, single-arm, open-label study **Study 04.3**: Phase II, multicenter, single-arm, open-label, extension study	**Induction:** 1.25 mg/m² twice daily for 14 consecutive days **Maintenance:** Monthly courses consisting of 7 days of treatment plus a follow-up period up to Day 28 or longer	4
AML-204	Phase II open-label, multicenter study	**Induction:** SC omacetaxine 2.5 mg/m² twice daily for 9 consecutive days every 28 (±3) days **Maintenance:** SC omacetaxine 2.5 mg/m² twice daily for 7 days every 28(±3) days	13
CGX-205	Open-label non-randomized PK study	1.25 mg/m^2 twice daily for 14 consecutive days 28-day cycles	21
CML-206	Retrospective collection of safety data	Variable (SC=43, IV=33)	43

7.3.2 Drug exposure

Table 12 summarizes the drug exposure. Variable dose regimens were administered to these patients due to dose reductions/modifications, shortening and lengthening of treatment cycles, leading to a wide range of variation in drug exposure. For example, CP-CML patients received as low as 20.1 mg/m^2 or as much as 429.2 mg/m^2 of accumulated

omacetaxine dose. The median dose exposure for these 131 patients was 101.1 mg/m^2, and the median cycles administered were 4.

Table 12 Total Exposure to Omacetaxine in Study Group 2

	Combined CML-202 and CML-203 Studies (SG2)			
	CP-CML (n=70)	**AP-CML (n=36)**	**BP-CML (n=25)**	**Combined (n=131)**
Duration of exposure (months)				
Mean (SD)	9.4 (7.6)	4.9 (5.9)	2.6 (3.1)	6.9 (7.0)
Median	8.0	2.7	1.7	4.5
Min-Max	0.3-34.6	0.5 – 28.0	0.1 - 14.0	0.1 – 34.6
Total number of cycles of exposure				
Mean (SD)	8 (6.7)	5 (5.4)	3 (2.4)	6 (6.2)
Median	6	3	2	4
Min-Max	1 – 31	1 - 29	1 – 12	1 - 31
Dose delivered during study (mg/m^2)				
Mean (SD)	161. 0 (102.9)	134.9 (144.3)	80.1 (79.9)	138.1 (115.5)
Median	138.0	85.8	55.4	101.1
Min-Max	20.1 – 429.2	32.2 – 814.4	7.6 - 393.5	7.6 - 814.4

At the time of data cut-off, 23 (18%) patients remained on study while 108 (82%) patients had discontinued the study treatment. The most common reasons for discontinuation were lack of response (45%), death (12%), withdrawal by subject (10%), adverse event (8%), other (7%) and non-compliance (<1%).

One hundred and nine (83%) patients received more than one cycle of therapy. Eighty-three (76%) of these patients had at least one delay in therapy. The mean number of cycle delays for patients receiving more than one cycle of therapy was 3 (SD=2.9) cycles with a median of 2 (range of 0 to11). Hematological toxicity accounted for 67% of all delays. Thrombocytopenia (31%) was the most common reason for delays in therapy followed by patient availability (21%) and pancytopenia (17%). Non-hematologic toxicities accounted for only 3% of treatment delays.

7.3.3 Adverse Events

One hundred and twenty nine (96.9%) of the patients in SG2 had ≥ 1 Treatment Emergent Adverse Events (TEAEs) with 111 (85%) having ≥ 1 CTCAE grade 3 or 4 TEAEs. Eight-nine percent CP-CML patients had grade 3 or 4 TEAEs compared to 78% in AP-CML and 84% in BP-CML patients, respectively. Twenty-five (19%) patients were reported to have a grade 5 TEAE. These patients are described in more detail in section 7.3.5.

The most common AEs were thrombocytopenia (60.3%), anemia (48.9%), diarrhea (42.7%), neutropenia (38.2%), fatigue (31.3%), pyrexia (29.8%), nausea (27.5%), asthenia (21.4%), headache (19.1%), arthralgia (16.8%), cough (16.8%), peripheral edema (16.0%), injection site erythema (16.0%), constipation (15.3%) and anorexia (14.5%). The most common grade 3 and 4 AEs were thrombocytopenia (55%), anemia (34.4%), and neutropenia (35.1%). See Table 13.

Table 13 Adverse Events (Grades 1-4) in ≥ 10% of Patients in Study Group 2

	CML-CP n = 70		CML-AP n = 36		CML-BP n= 25		Total n = 131	
Preferred Term	All Grade	grades 3/4	All Grade	grades 3/4	All Grade	grades 3/4	All Grade	grades 3/4
	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
Thrombocytopenia	74.3	65.7	50.0	47.2	36.0	36.0	60.3	55.0
Anaemia	64.3	44.3	38.9	27.8	20.0	16.0	48.9	34.4
Diarrhoea	42.9	1.4	41.7	11.1	44.0	8.0	42.7	5.3
Neutropenia	52.9	50.0	16.7	13.9	28.0	24.0	38.2	35.1
Fatigue	28.6	4.3	36.1	11.1	32.0	8.0	31.3	6.9
Pyrexia	25.7	1.4	27.8	0.0	40.0	4.0	29.0	1.5
Nausea	28.6	1.4	27.8	2.8	24.0	0.0	27.5	1.5
Asthenia	24.3	1.4	22.2	2.8	12.0	0.0	21.4	1.5
Headache	20.0	0.0	16.7	2.8	20.0	4.0	19.1	1.5
Arthralgia	20.0	1.4	11.1	0.0	16.0	0.0	16.8	0.8
Cough	12.9	1.4	19.4	0.0	24.0	0.0	16.8	0.8
Injection site erythema	22.9	0.0	11.1	0.0	4.0	0.0	16.0	0.0
Oedema peripheral	12.9	0.0	16.7	0.0	24.0	4.0	16.0	0.8
Constipation	14.3	0.0	8.3	0.0	28.0	0.0	15.3	0.0
Epistaxis	15.7	0.0	11.1	2.8	16.0	0.0	14.5	0.8
Anorexia	10.0	0.0	19.4	2.8	20.0	4.0	14.5	1.5
Leukopenia	21.4	20.0	8.3	5.6	0.0	0.0	13.7	12.2
Pain in extremity	14.3	0.0	13.9	2.8	12.0	8.0	13.7	2.3
Febrile neutropenia	8.6	8.6	16.7	13.9	24.0	20.0	13.7	12.2
Vomiting	11.4	0.0	11.1	0.0	20.0	0.0	13.0	0.0
Lymphopenia	21.4	20.0	0.0	0.0	0.0	0.0	11.5	10.7
Abdominal pain	8.6	0.0	16.7	0.0	12.0	0.0	11.5	0.0
Alopecia	14.3	0.0	5.6	0.0	8.0	0.0	10.7	0.0
Insomnia	11.4	0.0	0.0	0.0	12.0	0.0	8.4	0.0

7.3.4 Serious Adverse Events (SAEs)

One hundred and eighty-one SAEs were reported in 78 (59.5%) patients in Study Group 2. Thirty eight (54.3%) of these patients had CP-CML, 19 AP-CML (52.8%) and 21 (84.0%) BP-CML. The most frequent SAEs were febrile

neutropenia (10.7%), thrombocytopenia (10.7%), bone marrow failure (7.6%) and anemia (3.8%) (Table 14).

Table 14 SAEs in ≥ 2% of patients in Study Group 2

Preferred Term	# of SAEs
Febrile neutropenia	14 (10.7%)
Thrombocytopenia	14 (10.7%)
Bone marrow failure	10 (7.6%)
Anaemia	5 (3.8%)
Sepsis	5 (3.8%)
Diarrhoea	4 (3.1%)
Febrile bone marrow aplasia	4 (3.1%
Pyrexia	4 (3.1%
Neutropenia	3 (2.3%)
Pancytopenia	3 (2.3%)
Pneumonia	3 (2.3%)
Transfusion reaction	3 (2.3%)

7.3.5 Death

Twenty-seven (21%) of the patients who were enrolled on Study Group 2 had died at the time of data cut-off. These are summarized in Table 15 and Table 16.

Table 15 Deaths on CML 202

CML phase	# of Cycles	Reason for withdrawal	Cause of death
BP	2	Death	Pneumonia
BP	1	Death	Sepsis
AP	13	Adverse event	Renal failure chronic
BP	4	Death	Arrhythmia
BP	2	Progressive Disease	Pulmonary hemorrhage
BP	3	Progressive Disease	Disease progression
CP	13	Death	Cerebral hemorrhage
CP	5	Death	Unknown
AP	1	Death	Sepsis
BP	1	Progressive Disease	Leukostasis
CP	1	Progressive Disease	Bone marrow necrosis
CP	6	Adverse event	Sepsis
AP	3	Death	Pneumonia
CP	3	Death	Pyrexia
CP	3	Progressive Disease	Deep vein thrombosis
AP	5	Death	Death

BP	1	Death	Tumor lysis syndrome
CP	1	Progressive Disease	Cerebral hemorrhage

Table 16 Deaths on CML 203

CML Phase	# of Cycles	Reason for Withdrawal	Cause of Death
BP	3	Death	Disease progression
BP	2	Lack of Efficacy	Sepsis
BP	12	Death	Disease progression
BP	1	Progressive Disease	Disease progression
AP	1	Progressive Disease	Blast cell crisis
CP	6	Death	CML
AP	2	Death	Febrile neutropenia
BP	2	Death	Disease progression
BP	1	Death	Disease progression

Review of source data including CRFs revealed that 9 CML-AP and BP patients had pneumonia or pulmonary symptoms or insufficiency at the time of death. The exact nature of pulmonary involvement in these patients was not well defined based on the available data.

7.3.6 Laboratory findings

- Hyperglycemia

Administration of omacetaxine was associated with episodes of hyperglycemia. Sixteen TEAEs of hyperglycemia, increased blood glucose or diabetes were reported in 11 (8%) of patients in Study Group 2 None of these events was considered an SAE although 3 were grade 2, and 3 were grade 3. Eight (50%) of these events did require administration of appropriate medication.

FDA's review on blood glucose levels revealed that 64 (49%) patients with normal baseline blood glucose levels went on to develop hyperglycemia while on study. Twenty one (16%) of these subjects developed a CTCAE grade 2, 2 (2%) had grade 3 and 5 (4%) had grade 4 abnormality. In addition, 12 (9%) patients who had an abnormal level at baseline had further worsening of their blood Glucose levels.

- Hyperbilirubinemia

FDA's review of source data including CRFs reveal that 11 patients (8%) in Study Group 2 had elevated bilirubin levels or jaundice during therapy (CTCAE grade 1 or 2) reported by the investigators. One AP-CML patient with elevated bilirubin was

reported to have developed “hepatic failure” and subsequently died of other complications, although other concomitant hepatotoxic medications in this patient precluded a definitive attribution of omacetaxine to the hepatic failure.

In addition, 39 (30%) additional patients had a rise in their bilirubin levels during the course of their therapy. Twenty-one patients had an increase from normal at baseline to grade 1, 11 to grade 2, 5 to grade 3 and 2 to grade 4. The bilirubin levels in 21 of these patients had normalized by the end of therapy.

7.3.7 Cardiovascular toxicity

Omacetaxine has been under study in United States, Europe, and China for over 20 years. An intravenous preparation of omacetaxine was originally studied in patients with CML, AML and MDS but the development of this agent was delayed due to the emergence of TKIs and the side effect profile of this agent administered as intravenous bolus including dose limiting cardiovascular complications (hypotension)[7].

Seven patients (5%) were reported to have developed hypotensive episodes regardless of causality with four grade 2 and one grade 3 hypotension (Table 17). It should be noted that NCI CTC criteria for grade 2 hypotension would have required intervention for less than 24 hours with fluid replacement or other therapy but should have had no physiologic consequences.

Table 17 Hypotensive Episodes in Study Group 2

AE	Outcome	SAE	Tox Grade	Action required
Hypotension	Not Recovered/ Not Resolved	N	3	Non-Drug Therapy Required
Orthostatic hypotension	Not Recovered/ Not Resolved	N	1	Non-Drug Therapy Required
Orthostatic hypotension	Recovered/Resolved	N	1	None
Hypotension	Recovered/Resolved	N	2	None
Hypotension	Recovered/Resolved	Y	2	Hospitalization
Hypotension	Recovered/Resolved	N	2	Non-Drug Therapy Required
Hypotension	Not Recovered/ Not Resolved	N	2	None

Twenty-one patients in SG2 were reported to have 37 episodes of cardiac rhythm abnormalities. Fifteen episodes in 9 patients were reported to be ≥ grade 2. Eight of these episodes were reported as self-resolving. Table 18 lists all episodes that were ≥ grade 2, were rated as an SAE or required treatment.

Table 18 Patients with Arrhythmias in Study Group 2

AE	Outcome	SAE	Tox Grade	Action required
Arrhythmia	Fatal	Y	5	Hospitalization
Arrhythmia	Recovered/Resolved	Y	4	Hospitalization
Tachycardia	Unknown	U	3	Unknown
Extrasystoles	Recovered/Resolved	Y	2	Medication Required
Tachycardia	Not Recovered/ Not Resolved	N	3	Medication Required
Sinus tachycardia	Recovered/Resolved	N	2	Medication Required
Atrial fibrillation	Recovered/Resolved	N	2	Medication Required

FDA's review on the source data including CRFs did not reveal cardiovascular complications as serious as those reported for the intravenous formulation.

8. Summary

This NDA submission is based on a single efficacy study, CGX-635-CML-202 (CML-202), in 66 patients with CML who had failure of imatinib therapy and had the T315I mutation.

Study CML-202 was planned to enroll 100 patients. However, the NDA submission only included the efficacy data from 66 patients. The Applicant continued to enroll additional patients after the data cut-off for these 66 patients.

The indication sought for omacetaxine is for the treatment of CML patients with Bcr-Abl T315I mutation. However, there is no commercially available assay for the detection of this mutation and the Applicant has not submitted any data related to the assay methods to FDA's CDRH. In addition, 35% of patients had no confirmation of Bcr-Abl T315I mutation status by the central laboratory at the time of enrollment, a required study entry criterion

The response rate observed in the efficacy study was low. For the chronic phase cohort of 40 patients, the MCyR rate was 15% (10% CCyR + 5% PCyR) with a median of

duration of response of 7.7 months. For the accelerated phase cohort of 16 patients, the MCyR rate was 6.3% and CHR rate was 31.3% with a median of duration of response of 22 weeks. There were no responders in the BP cohort.

The main toxicities were related to myelosuppression with thromobocytopenia, neutropenia and anemia.

ODAC advice is sought on the adequacy of the sample size, the clinical significance of the observed responses and their duration in the intended patient population, and the benefit:risk ratio for omacetaxine treatment in patients with CML and the T315I mutation after failure of imatinib therapy.

9. References

[1] American Cancer Society.: Cancer Facts and Figures 2009. Atlanta, Ga: American Cancer Society, 2009.

[2] Fialkow, P. J., Jacobson, R. J., and Papayannopoulou, T. Chronic myelocytic leukemia: clonal origin in a stem cell common to the granulocyte, erythrocyte, platelet, and monocyte/macrophage. *Am. J. Med.* 1997; 63*:* 125–130.

[3] Vardiman JW, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. *Blood* 2002;100(7):2292-302.

[4] Speck B, Bortin MM, Champlin R, et al. Allogeneic bone-marrow transplantation for chronic myelogenous leukaemia. *Lancet*. 1984;1:665-668.

[5] Gorre ME, Mohammed M, Ellwood K, Hsu N, Paquette R, Rao PN, Sawyers CL. Clinical resistance to STI-571 cancer therapy caused by BCR-ABL gene mutation or amplification. *Science* 2001; 3;293(5531):876-80.

[6] Nicolini FE, Mauro MJ, Martinelli G, Kim DW, Soverini S, Muller MC, Hochhaus A, Cortes J, Chuah C, Dufva IH, Apperley JF, Yagasaki F, Pearson JD, Peter S, Sanz Rodriguez C, Preudhomme C, Giles F, Goldman JM, Zhou W. Epidemiological study on survival of chronic myeloid leukemia (CML) and Ph+ acute lymphoblastic leukemia (ALL) patients with BCR-ABL T315I mutation. *Blood,* Dec 2009; 114: 5271 – 5278

[7] O'Brien S, Kantarjian H., Keating M., Beran M., Koller C., Robertson L.E., Hester J., Rios M., Andreeff M., and Talpaz M. Homoharringtonine Therapy Induces Responses in Patients With Chronic Myelogenous Leukemia in Late Chronic Phase. Blood, Vol 86, No 9 (November I), 1995: pp 3322-3326.